REMARKS

In the Office Action, the Examiner objected to claim 13; rejected claims 1, 3, 4, 6, 7, and 12-22 under 35 U.S.C. § 112, first paragraph; rejected claims 1, 3, 4, 6, 7, and 12-22 under 35 U.S.C. § 112, second paragraph; rejected claims 1, 3, 4, 7, 12, 13 and 15-22 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,495,127B to Wallace et al.; rejected claims 1, 3, 4, 7, 12, 13 and 15-22 under 35 U.S.C. § 103(a) as being unpatentable over Wallace et al. in view of U.S. Patent No. 6,547,806 to Ding and U.S. Patent No. 6,471,993 to Shastri et al.; rejected claims rejected claims 1, 3, 4, 7, 12, 13 and 15-22 under 35 U.S.C. § 103(a) as being unpatentable over Wallace et al. in view of published U.S. Patent Application No. 2003/0095993 to Bentz et al., Ding, and Shastri et al.

Applicants have amended claims 1, 3, 13 and 14; cancelled claims 8-12, 15, 17, 19 and 21; and add new claims 23-28. Claims 1, 3, 4, 7, 13, 14, 16, 18, 20 and 22-28 are pending in the patent application.

By way of background, Applicants' disclosure is directed toward, among other things, a novel tissue adhesive composition having a mesh or fibers embedded therein for additional strength, for example. Tissue adhesives or solders must have sufficient mechanical properties to strongly join tissues in surgical applications (see Applicants' specification at page 1, lines 8-9). Tissue adhesives should also be non-toxic (id., lines 10-14). In

laser-assisted welding applications disclosed herein, tissues are joined together, the adhesive is applied, melted, and as it cools and solidifies, the tissues are bonded together.

Applicants' novel composition incorporating embedded fibers or mesh satisfies the above-described requirements of tissue adhesives. The composition is collagen based, and is therefore non-toxic. Moreover, the high concentration of derivatized collagen is believed to provide a greater number of linkages so that upon exposure to laser light of a suitable wavelength, increased crosslinking with surrounding tissue is believed to occur (specification at page 3, lines 1-3; page 4, lines 3-6). Accordingly, a tissue adhesive having improved cohesive strength (Id.), and exceptional tensile strength of 1000g/cm^2 (specification at page 14, lines 17-21) can be achieved. By attaching carboxyl groups and carboxyl/thiol groups through derivatization, it is believed that the net negative charge of the adhesive ionically interacts with the positively charged proteins in tissues so that the adhesive is soluble at physiologic pH (page 9, lines 8-12), and the adhesive will dissolve within the body over time. An embedded mesh or fibers in the adhesive composition can provide additional strength, flexibility and uniform heating or electrical properties to an adhesive patch (see Applicants' specification at page 16, lines 3-15.)

Applicants realized, however, that derivatized collagen solutions saturate at about 10% or 100 mg/ml (e.g., page 10, lines

15-16), far short of the concentration believed necessary to provide a sufficient number of cross-linking sites, as noted above. In light of the limited solubility of known derivatized collagen-based solutions, Applicants developed a unique process to make their novel tissue adhesive. As described in the specification, derivatized collagen was successively added to a derivatized collagen solution, and the solution was heated to 50 degrees Celsius, for example (e.g., page 10, lines 16-23). With each addition, the concentration is increased until a desired concentration is achieved (e.g., page 10, lines 18-22). Heating the solution is believed to cause the derivatized collagen to break down into smaller molecular weight units. Accordingly, as further discussed in the specification, a gelatinized and derivatized collagen is obtained (e.g., page 10, line 16 - page 11, line 1).

Gelatin, as generally understood, is obtained through a series of complex high temperature heating steps for extended periods of time. For example, as discussed in the attached text to Veis ("The Macromolecular Chemistry of Gelatin, Academic Press, 1964, pp. 186-219) gelatin is prepared by heating collagen at relatively high temperatures for extended periods of time (see page 212, e.g., two hours at 60 degrees Celsius; three hours at 80 degrees Celsius; and two hours at 93 degrees Celsius). In contrast, as noted above, carboxyl/thiol derivatized collagen undergoes a series of brief heating steps at 50 degrees Celsius

(e.g., see Applicants' specification at page 10, lines 18-22). Accordingly, prior art teachings of gelatin as in Veis, therefore, fail to teach or suggest high concentration (i.e., in the range of 300 mg/ml to 800 mg/ml), gelatinized collagen, which is derivatized with a carboxyl group or with both carboxyl and thiol groups.

Moreover, as indicated at page 2 in an Office Action dated November 19, 2003, in copending application Serial No. 09/973,332, Applicants previously amended claim 1 in that case, covering non-derivatized collagen was deemed to constitute a substantial change in subject matter from originally filed claim 1 in that application directed toward derivatized collagen. Thus, the Examiner apparently acknowledges that non-derivatized collagen material, such as gelatin, is distinguishable over derivatized collagen material.

Further, the Examiner maintains at page 5 of the final Office Action in the present application, that whether a particular derivatized collagen material may be used as a tissue adhesive is unpredictable and requires undue experimentation. Since such unpredictability should extend to compositions including gelatin, Applicants submit that their claimed tissue adhesive patch is novel and non-obvious over prior art teachings of gelatin for this reason as well.

Turning to the claims, independent claims 1 and 14 and new claim 23 each recite a tissue adhesive patch including a mesh.

Amended claim 1 requires that the mesh including a polymer selected from the group consisting of nylon, polyester and polycarbonate, support for which can be found in the specification, for example, at page 16, lines 3-6. Amended claim 14 recites a mesh including carbon (see, for example, the above cited portion of the specification at page 16, lines 3-6), and new claim 23 requires that the mesh include metal (Id.)

Claim 3 and new claims 25 and 27 are directed toward a tissue adhesive patch including a plurality of fibers. In claim 3, the fibers include a polymer selected from the group consisting of nylon, polyester and polycarbonate (see, for example, Applicants' specification at page 16, lines 11-13). Fibers including carbon, as recited in new claim 25, as well as fibers including metal required by new claim 27, are discussed in the specification at page 16, line 13. Moreover, exemplary support for collagen fibrils, as recited in amended claim 13, can be found in the specification at page 17, lines 18-21.

Each of independent claims 1, 3, 13, 14, 23, 25 and 27 has also been amended to reflect the above-described features of Applicants' novel composition. Namely, as amended, each of these claims recites a tissue adhesive, comprising collagen. The concentration of collagen in the adhesive being 300 mg/ml to 800 mg/ml. Support for the claimed range of concentrations may be found, for example, in the specification at page 3, lines 5-7. Amended claim 1 also recites that the collagen is derivatized with

a COO^- functional group. Support for this limitation can be found, for example, in the specification at page 10, lines 6-8. In addition, the collagen is gelatinized, support for which can be found, for example, in the specification at page 10, line 16 - page 11, line 4.

Further, each of new claims 16, 20, 22, 24, 26 and 28 requires that that the collagen is also derivatized with an SH^-, i.e., thiol group (see, for example, the specification at page 10, lines 6-8).

At the outset, Applicants respectfully point out that the Examiner's rejections with respect to claims 12, 15, 17, 19 and 21 is moot in light of the cancellation of these claims.

Turning to the objections and rejections of the claims, Applicants respectfully submit that the Examiner's objection of claim 13 is moot in light of the amendment to this claim.

Applicants respectfully traverse the Examiner's rejections of claims 1, 3, 4, 6, 7, and 12-22 under 35 U.S.C. § 112, first paragraph, as well as the rejection of these claims under 35 U.S.C. § 112, second paragraph. The Examiner has apparently addressed the same claim language and made similar arguments in rejecting the claims under both first and second paragraphs of Section 112. Accordingly, these rejections will be collectively addressed below.

In rejecting the claims under Section 112, the Examiner contends that language directed toward the concentration of

collagen, and well as use of the term "material" (see final Office Action at pages 2, 3, 6 and 7) constitutes new matter and does not otherwise satisfy the first and second paragraphs of Section 112. Although Applicants respectfully disagree with the Examiner's conclusions, Applicants have amended claims 1, 3, 13 and 14 to delete the term "material" and have redrafted language related to the concentration of collagen consistent with the Examiner's suggestion at page 7, lines 1-2 and lines 13-16.

Applicants also respectfully disagree with the Examiner's assertion at pages 4 and 6 of the Office Action, that "'the specification only teaches 'collagen' fibers", and thus the claims can only be limited to patches including such fibers. As noted above, the specification at page 16, lines 11-15, describes:

> a plurality of fibers 810 (made of biologically compatible and non-irritating material such as a polymer (e.g., nylon, polyester, polycarbonate), carbon or metal can be dispersed throughout layer 620.

Thus, fibers other than collagen are disclosed in Applicants' specification, thereby providing support for the changes to claim 3, as well as new claims 25 and 27.

Applicants further respectfully submit that the Examiner's arguments regarding enablement and the scope of functional groups covered by the claims is rendered moot in light of Applicants' amendment. Namely, each of independent claims 1, 3, 13, 14, 23, 25 and 27 requires derivatiziation with a carboxyl group, support for which has been discussed extensively above. These claim

changes are consistent with the Examiner's suggested claim language at page 5, lines 18-20.

Before addressing the Examiner's rejections under Section 103, Applicants respectfully note that claim 14 was not rejected based upon prior art. In Applicants amendment dated July 21, 2003, claim 14 was amended to recite a tissue adhesive patch including a mesh structure including carbon or metal and derivatized collagen having a particular range of concentrations. By this amendment, Applicants have incorporated subject matter of dependent claim 21 requiring carboxyl derivatization into claim 14. Claim 21 has been cancelled. Applicants have also made amendments, discussed above, in connection with the Examiner's rejection under Section 112, and have amended the claim to require carbon, as opposed to carbon or metal, as recited previously. Claim 14, as further noted above, also requires collagen that has been gelatinized. These changes are not deemed to raise new issues. In the absence of any prior art-based rejection of claim 14, Applicants submit that claim 14 and claim 22, which depends therefrom, are distinguishable over the applied references and these claims are in condition for allowance.

Applicants respectfully traverse the Examiner's rejection of claims 1, 3, 4, 7, 12, 13 and 15-22 under 35 U.S.C. § 103(a) as being unpatentable over Wallace et al. In citing the previous Office Action dated April 22, 2003, the Examiner apparently contends that Wallace et al. teaches each limitation of these

claims except the required concentration of collagen, which the Examiner asserts is "merely routine optimization of one of skill in the art" (Office Action at page 8). Applicants respectfully disagree. As discussed in greater detail below, not only is the claimed range of concentrations non-obvious, but the Wallace et al. also fails to disclose the mesh recited in claims 1 and 23, as well as the fibers recited in claims 3, 13, 25 and 27.

As noted above, and discussed in Applicants' specification (see page 10, lines 13-22) since collagen typically becomes saturated at less than 10%, a new technique was developed to obtain carboxyl-derivatized collagen with the claimed concentration of 300 mg/ml to 800 mg/ml. None of the cited references even recognizes that collagen solutions saturate at relatively low concentrations. Accordingly, given the difficulties associated with achieving the claimed concentration, and, moreover, since the Examiner acknowledges that Wallace et al. is entirely silent with respect to the claimed concentrations, Applicants respectfully submit that their claimed tissue adhesive patch, as recited in claims 1, 3, 13, 23, 25 and 27 would not have been obvious to one of ordinary skill.

Moreover, the Examiner maintains in an Office Action dated August 22, 2003, in related application Serial No. 09/973,332, that whether a particular derivatized collagen material, at a particular concentration, may be used as a tissue adhesive is unpredictable and requires undue experimentation (see pages 3, 4

and 6 of the August 22, 2003 Office Action). Given such unpredictability and undue experimentation as acknowledged by the Examiner, Applicants respectfully submit that providing the claimed concentrations, as recited in claims 1, 3, 13, 23, 25 and 27 could not be achieved through mere routine optimization of one or skill in the art. These claims are therefore not obvious over Wallace et al. for this reason as well.

Wallace et al. also suffers from other deficiencies. Claims 1, 3, 13, 23, 25 and 27 each require collagen that is derivatized with a carboxyl functional group, a feature neither taught nor suggested by any of the applied references. Carboxyl derivatization, was recited in dependent claims 15, 17, 19 and 21, which were added by amendment in Applicants' reply dated July 21, 2003. The subject matter of claims 15, 17, 19 and 21 was incorporated into claims 1, 3, 13, 23, 25 and 27. Even though claims 15, 17, 19 and 21 were rejected, the final Office Action does not cite any teaching in any of the applied prior art in support of the Examiner's assertion that these claims are unpatentable. Claims 15, 17, 19 and 21 are therefore deemed to recite allowable subject matter in light of the failure of the final Office Action to adequately address these claims. Accordingly, at least for this reason, claims 1, 3, 13, 23, 25 and 27, which recite the subject of claims 15, 17, 19 and 21 are also deemed allowable over Wallace et al.

Further, as discussed in Applicants' specification, carboxyl

derivatization is achieved through reaction of carboxyl groups with free amine groups on a native collagen molecule. Once reacted, the free amine groups are replaced with carboxyl groups. As discussed in Applicants Amendment dated July 21, 2003, however, Wallace et al. expressly teaches that "[d]erivatives of collagen … *which may not contain free, reactive amino groups … are also not preferred*" (Emphasis added) (col. 13, lines 54-58). Thus, in this respect, Wallace et al. clearly teaches away from Applicants' claimed combination including carboxyl derivatized collagen, as recited in claims 1, 3, 13, 23, 25 and 27.

With respect to mesh-directed claims 1 and 23. Contrary to the Examiner's assertions, Wallace et al. does not teach "a mesh-like core … [including] a polymer selected from the group consisting of nylon, polyester, or polycarbonate" (see Office Action at page 10). The portion of Wallace et al. cited by the Examiner for teaching a "mesh-like core", col. 7, lines 43-47, discloses use of polyesters as "core materials in the practice of the present invention." The "core" as defined by Wallace et al. is the "non-reactive remainder of the compound" (col. 6, lines 45-48). Thus, the "core" referred to in the Office Action, is not a mesh structure, but part of a polymer molecule. Respectfully, Applicants fail to see how disclosure of a portion of a polymer molecule can somehow constitute a mesh structure, as claimed herein.

Moreover, what little disclosure of a mesh in Wallace et al.

is vague and incomplete. The reference only states that meshes can be coated with "components", but is silent as to what these components are or the extent a mesh would be coated. Such minimal teachings are insufficient to establish that Applicants claimed combination including a mesh is obvious.

In addition, with respect to claims 3, 13, 25 and 27 reciting a plurality of fibers, only claim 13 recites a tissue adhesive patch including a plurality of *collagen* fibrils, while claims 3, 15, 25 and 27 recite fibers including specific polymers. In formulating the rejection based on Wallace et al. in both the first Office Action and the final Office Action, the Examiner apparently relies on teachings at column 10, lines 43-46 and col. 18, lines 4-8 in arguing that the reference teaches the claimed tissue adhesive patch including collagen fibers. Even if true, such teachings would fail to render claims 3, 25 and 27 obvious (claim 3 recites fibers including a polymer, and claims 25 and 27 recite carbon and metal fibers, respectively). In regard to claim 13, the cited portion of Wallace et al. merely suggests that collagen fibers could be added to a gel based on 60% aqueous (w/v) COH102/COH206, not derivatized and gelatinized collagen. Accordingly, there is also simply no teaching or suggestion in Wallace et al. of the claimed combination including a tissue adhesive patch including collagen fibrils embedded in a carboxyl-derivatized collagen tissue adhesive, as recited in claim 13.

Applicants further note that Wallace et al. discloses use of

Vicryl, "a copolymer of glycolic acid and lactic acid" in a gel apparently containing methylated collagen (col. 27, lines 26-35). Such teachings, however, fail to suggest Applicants claimed patch including carboxyl derivatized collagen, which is also gelatinized, and having a concentration which is 300 mg/ml (30%) to 800 meg/ml (80%), nor the fibers and mesh structures, as recited in independent claims 1, 3, 13, 23, 25 and 27.

In light of the above-described deficiencies of Wallace et al., Applicants submit that independent claims 1, 3, 13, 23, 25 and 27 are allowable over the applied reference. Moreover, claim 16 is allowable at least due to its dependence from claim 1; claims 4, 7 and 18 are allowable at least due to their dependence from claim 3; claim 20 is allowable at least due to its dependence from claim 13; and claims 24, 26 and 28 are allowable at least due to their dependence from claims 23, 25 and 27, respectively. Applicants note that claim 22 has been amended to depend from claim 14, which was not rejected over Wallace et al. alone or any other reference. As noted above, therefore, claims 14 and 22 are considered allowable.

Applicants respectfully traverse the Examiner's rejection of claims 1, 3, 4, 7, 12, 13 and 15-22 under 35 U.S.C. § 103(a) as being unpatentable over Wallace et al., in view of Ding and Shastri et al. At the outset, Applicants note that in this rejection, as in the other rejections based upon prior art, the final Office Action does not even address the subject matter of

claims 1, 3, 13, 23, 25 and 27 requiring collagen that is derivatized with a carboxyl functional group. As noted above, carboxyl derivatization, was recited in dependent claims 15, 17, 19 and 21, and this subject matter was incorporated into claims 1, 3, 13, 23, 25 and 27. Even though claims 15, 17, 19 and 21 were rejected, the final Office Action does not point to any teaching in any of the applied prior art in support of the Examiner's assertion that these claims are unpatentable. Claims 15, 17, 19 and 21 are therefore deemed to recite allowable subject matter in light of the failure of the final Office Action to adequately address these claims. At least for this reason, claims 1, 3, 13, 23, 25 and 27, which recite the subject of claims 15, 17, 19 and 21 are also deemed allowable over Wallace et al., Ding and Shastri et al. at least for this reason.

In formulating the rejection under Section 103 in view of Wallace et al., Ding and Shastri et al., the Examiner relies upon assertions made in the Office Action dated April 22, 2003. Applicants have previously addressed the shortcomings of Wallace et al. In the April 22, 2003 Office Action, the Examiner contends that Ding teaches carbon or metal wires and cites col. 5, lines 6-8. The Examiner also asserts that Ding discloses carbon fiber reinforced with a biocompatible resin at col. 5, lines 23-27. Upon careful examination of what Ding actually teaches, Applicants respectfully note that the reference teaches a sealing member 40 which acts to plug a hole a blood vessel 60. Sealing member 40 is

not a tissue adhesive and does not constitute a tissue adhesive patch. Such non-analogous teachings fail to render Ding combinable in the manner proposed by the Examiner.

Applicants further note that the Examiner's reliance in Shastri et al. of microvoids in a matrix clearly teaches away from Applicants invention as recited in claims 1, 3, 13, 23, 25 and 27. A void, as generally understood, connotes the absence of any material. Such teachings of voids cannot render the obvious the claimed combination including the *presence* of fibers in claims 1 and 23, as well as the *presence* of a mesh structure in claims 3, 13, 25 and 27.

Moreover, neither Ding nor Shastri et al. teaches or suggests the claimed tissue adhesive patch including a tissue adhesive having collagen, which is gelatinized, derivatized with a carboxyl group, and in a concentration of 300 mg/ml to 800 mg/ml. Accordingly, Ding and Shastri et al. both fail to overcome the above-described deficiencies of Wallace et al., and claims 1, 3, 13, 23, 25 and 27. In addition, claim 16 is allowable at least due to its dependence from claim 1; claims 4, 7 and 18 are allowable at least due to their dependence from claim 3; claim 20 is allowable at least due to its dependence from claim 13; and claims 24, 26 and 28 are allowable at least due to their dependence from claims 23, 25 and 27, respectively. As noted above, claim 22 has been amended to depend from claim 14, which was not rejected over prior art. Claims 14 and 22 are therefore

considered allowable.

Applicants respectfully traverse the Examiner's rejection of claims 1, 3, 4, 7, 12, 13 and 15-22 under 35 U.S.C. § 103(a) as being unpatentable over Wallace et al. in view of Bentz et al., Ding, and Shastri et al. In formulating this rejection, the Examiner has cited the same teachings in Wallace et al., Ding and Shastri et al. discussed above, but has also relied upon Bentz et al. allegedly for teaching a collagen concentration between 300 mg/ml and 800 mg/ml. Bentz et al. does not disclose collagen *per se*, but "denatured collagen or gelatin." Further, Bentz et al. is entirely silent as to derivatizing such material with a carboxyl functional group. Moreover, as pointed out by the Examiner, "determining whether any and all functional groups could elicit tissue cohesion and adhesion qualities ... wold require undue experimentation without reasonable expectation of success by one of skill in the art" (final Office Action at page 5). Given such unpredictability in determining whether derivatization with a given functional group, such as a carboxyl group, could yield a suitable tissue adhesive, Applicants submit that it would not be readily apparent to one of ordinary skill to derivatize the gelatin of Bentz et al.

Further, as note above, at page 2 in an Office Action dated November 19, 2003, in co-pending application Serial No. 09/973,332, Applicants previously amended claim 1 in that case covered non-derivatized collagen and was deemed by the Examiner to

constitute a substantial change in subject matter from originally filed claim 1 directed toward derivatized collagen. Thus, the Examiner apparently acknowledges that non-derivatized material is distinguishable and apparently non-obvious over derivatized collagen material.

Even if one of ordinary skill could derivatize the Bentz et al. gelatin, the resulting combination would still fail to suggest Applicants claimed adhesive including *gelatinized collagen*. As noted above, gelatin is obtained through an arduous process of heating collagen at relatively high temperatures 60, 80 and 93 degrees Celsius for extended periods of hours at a time (see discussion above of page 212 of Veis). In contrast, as discussed in the specification, Applicants' gelatinized collagen is realized through brief, but repeated heating steps of 50 degrees Celsius lasting seconds (e.g., see Applicants' specification at page 10, lines 18-22). Applicants' short heating steps at relatively low temperatures therefore yield a collagen-based material different than conventional gelatin described in Bentz et al. Thus, gelatin, as described in Bentz et al. is intrinsically different than Applicants' claimed gelatinized and derivatized collagen.

Bentz et al., therefore, fails to overcome the above-described shorting comings of Wallace et al., Ding and Shastri et al., and claims 1, 3, 13, 23, 25 and 27 are allowable over the applied references. Also, claim 16 is allowable at least due to its dependence from claim 1; claims 4, 7 and 18 are allowable at

least due to their dependence from claim 3; claim 20 is allowable at least due to its dependence from claim 13; and claims 24, 26 and 28 are allowable at least due to their dependence from claims 23, 25 and 27, respectively. As further discussed above, claims 14 and 22 are considered allowable in light of the absence of any prior art rejection of these claims.

Applicants respectfully submit that their proposed amendment pursuant to 37 C.F.R. § 1.116 does not raise new issues requiring further consideration and/or search. For example, Applicants claim changes reflect proposed language by the Examiner in connection with the rejections under 35 U.S.C. § 112, first and second paragraph. Moreover, Applicant has incorporated subject related to carboxyl derivatization into claims 1, 3, 13, 14, 23, 25 and 27 that was previously recited in dependent claims 15, 17, 19 and 21. In addition, language of new independent claims 23, 25 and 27 tracks language founds in claims 1, 13 and 14. Thus, new claims 23, 25 and 27 are not deemed to raise new issues either. Claims 24, 26 and 28, which respectively depend from claims 23, 25 and 27 are also not deemed to raise new issues, especially since new claims 24, 26 and 28 are directed to thiol derivatiziation which is also recited in claims 16, 20 and 22.

Further, as discussed above, Applicants claim changes place the present application in condition for allowance. Accordingly, entry of Applicants' amendment after final, and a timely issuance of a Notice of Allowance are earnestly requested.

09/973,385

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 02-0900.

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Respectfully submitted,

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